Medical and Pediatric Oncology 29:146–151 (1997)

PROCEEDINGS OF THE TUMOR BOARD OF RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER, CHICAGO, ILLINOIS

Jules E. Harris, MD, Series Editor*

Transformation of Chronic Lymphocytic Leukemia to Immunoblastic Lymphoma (Richter's Syndrome)

Homayoun Shahidi, MD,[1] William T. Leslie, MD,[1] Norman L. Wool, MD,[2] and Stephanie A. Gregory, MD[1]

INTRODUCTION

In January 1987, a 70-year-old black male was referred for evaluation of lymphadenopathy and persistent lymphocytosis. Except for a history of a 15 lb weight loss in the preceding 4 months, his medical history was noncontributory. On examination he was found to have bilateral adenopathy involving the cervical, axillary, and inguinal nodes. There was no palpable hepatosplenomegaly. A complete blood count showed a hemoglobin of 12 g/dl, platelet count of 149×10^9/l, and white blood cell count of 13.5×10^9/l with 90% lymphocytes and 10% neutrophils. A bone marrow examination revealed a hypercellular marrow with an infiltration of small lymphocytes comprising 78% of the nucleated marrow cells. There were no karyotypic abnormalities. On immunophenotypic analysis, the cells expressed CD5, CD19, CD20, HLA-DR, and monotypic IgM-κ (dim immunofluorescence). Computed tomography (CT) of the chest, abdomen, and pelvis disclosed multiple enlarged nodes and normal liver and spleen. A diagnosis of B-cell chronic lymphocytic leukemia (CLL) (Rai stage I) was made. No cytotoxic treatment was started and the patient was followed.

One month later, he developed a mass in the left groin. This mass had appeared over a period of 2 weeks and measured 15 × 5 cm. An excisional biopsy of the mass was consistent with large-cell lymphoma (Fig. 1). The patient received 3 cycles of chemotherapy with ProMACE-CytaBOM. (Cyclophosphamide 650 mg/M^2 IV, doxorubicin 25 mg/M^2 IV, etoposide 120 mg/M^2 IV, cytarabine 300 mg/M^2 IV, bleomycin 5 mg/M^2 IV, vincristine 1.4 mg/M^2 IV, methotrexate 120 mg/M^2 IV, prednisone 75 mg PO qod) administered at 21 day intervals. The therapy was terminated due to gram-negative sepsis, but the patient did respond with a marked reduction in the size of the lymph nodes. From July 1987 to June 1988, he was treated with biweekly chlorambucil and prednisone. He then remained stable off all therapy until 1993.

In August 1993, the patient developed progressive lymphocytosis and generalized lymphadenopathy (Fig. 2). A CT scan of the abdomen showed marked enlargement of the retroperitoneal and mesenteric lymph nodes. He was treated with monthly cycles of fludarabine (25 mg/M^2/day for 5 days) for 5 months, and had a complete nodal remission.

In February 1995, he presented with increasing lymphocytosis. His white blood cell count was 62×10^9/l with 38% prolymphocytes. He also had hepatomegaly and an axillary node measuring 10 × 10 cm. He was treated with the CHOP (cyclophoshamide 750 mg/M^2 IV day 1, doxorubicin 50 mg/M^2 IV day 1, vincristine 1.4 mg/M^2 IV day 1, prednisone 100 mg PO gd days 1–5) regimen and local radiation therapy. External beam radiation was given to the axillary node to a dose of 3,000 cGy without any decrease in the size of the node.

In April 1995, he died of gram-negative sepsis. An autopsy revealed massive generalized lymphadenopathy. The histologic examination of the lymph nodes showed large-cell immunoblastic lymphoma.

DISCUSSION

William T. Leslie, MD (Attending Physician, Rush Cancer Institute)

CLL is an indolent hematopoietic malignancy characterized by a clonal accumulation of mature-appearing small lymphocytes [1]. It accounts for approximately 9%

[1]Section of Hematology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; [2]Department of General Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

*Correspondence to: Jules E. Harris, MD, Section of Medical Oncology, Rush Medical College, 1725 West Harrison Street, Suite 821, Chicago, IL 60612-3824.

Received 30 December 1996; Accepted 23 January 1997

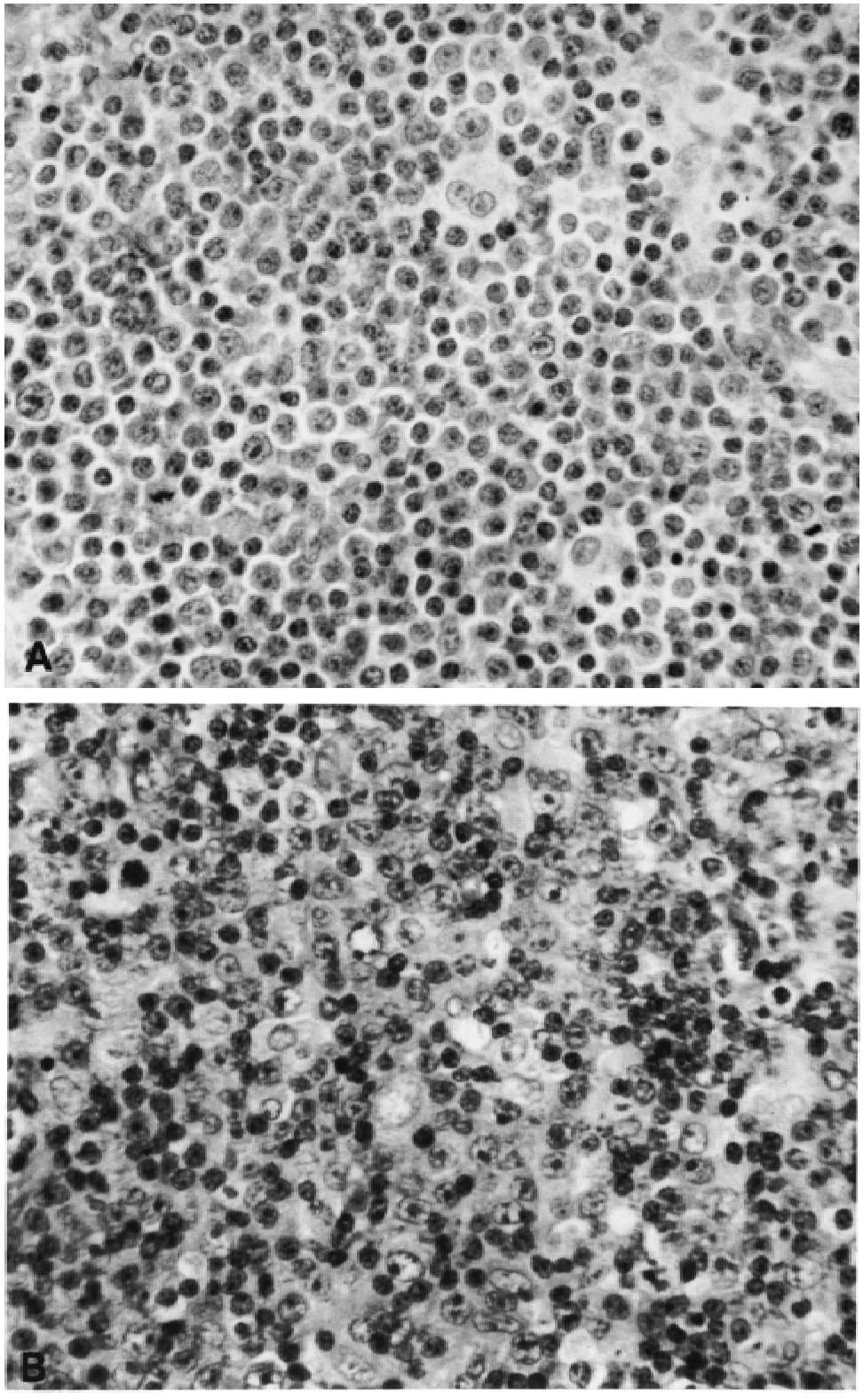

Fig. 1. Photomicrograph of lymph node biopsy specimen demonstrating an infiltrate of lymphoplasmacytic cells **(A)** and a large lymphoid cell infiltrate **(B).**

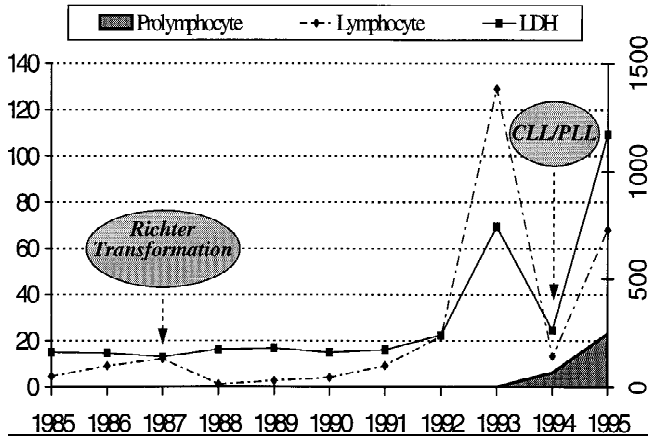

Fig. 2. Transformation of CLL to large-cell lymphoma. Absolute lymphocyte count (left axis) and LDH levels (right axis) during the patient's clinical course.

of all cancers in whites, but only 0.7% of cancers in African Americans [2]. Although CLL is often considered to be a relatively ''benign'' disease, the median survival of 5–7 years is counterbalanced by recurrent infections, autoimmune cytopenias, and secondary malignancies such as skin or lung cancer. More life-threatening clinical features include disease progression or transformation to an aggressive B-cell lineage lymphoma [1].

The clinical staging systems identify three broad groups of patients with respect to overall survival: low risk (Rai stage 0), intermediate risk (Rai stages I and II), and high risk (Rai stages III and IV) [1]. Although the clinical stage is the best predictor of survival for high-risk CLL, it provides insufficient information about the likelihood and rapidity of disease progression in low- to intermediate-risk CLL patients. Additional prognostic factors including patterns of bone marrow infiltration, immunophenotyping and cytogenetics, and lymphocyte doubling time have been devised to better predict the clinical course of the disease. Using these prognostic factors, cytotoxic treatment can be deferred in patients with low- or intermediate-risk CLL who would not benefit from early treatment [1].

Except in a small subgroup of patients with low lymphocyte counts and a normal hemoglobin concentration (''smoldering CLL''), all patients with CLL will have a progressive disorder. In approximately 10% of patients, transformation to a more aggressive B-cell malignancy occurs [3]. Patients can develop diffuse large-cell lymphoma (Richter's syndrome), prolymphocytic leukemia (CLL/PL), or rarely, acute lymphoblastic leukemia or multiple myeloma. Whether these malignancies represent a clonal evolution or a concurrent second neoplasm remains to be determined [3]. Clinically, however, transformation of CLL to a high-grade malignancy is associated with resistance to treatment, an aggressive course, and a shorter survival.

RICHTER'S TRANSFORMATION

Homayoun Shahidi, MD (Fellow, Hematology/ Oncology, Rush Cancer Institute)

Four years after the first formal description of CLL as a distinct clinical entity [4], Maurice N. Richter [5] described a patient with CLL who developed a rapidly fatal lymphoma. At autopsy, the patient had massive abdominal nodes showing two types of pathology: 1) changes consistent with small lymphocytic lymphoma (SLL) and 2) ''reticulum cell lymphoma.'' Approximately 40 years later, Lortholary et al. [6] introduced the term Richter's syndrome to describe the phenomenon of histologic progression of CLL to diffuse large-cell lymphoma.

The estimated incidence of Richter's syndrome has ranged from 3 to 15%. A recent report of 39 cases of 1,374 patients with CLL from a single institution suggests a true incidence in the 3–5% range [7]. Autopsy series, however, reveal evidence of transformation to a diffuse large-cell lymphoma in 25% of the patients with SLL, the lymph node counterpart of CLL [8]. Although most cases of large-cell lymphoma develop after several years, synchronous presentations have been described.

The development of Richter's transformation is independent of the stage, the type of therapy, or the response to therapy. In a report by Robertson et al. [7], 10 patients with Richter's syndrome (25%) had no evidence of CLL at the time of transformation. Three of these 10 were also free of disease as assessed by molecular genetic techniques. Despite treatment, the median survival was only 5 months after transformation. The study found that patients with complex karyotypic abnormalities were more likely to progress to a large-cell lymphoma [7].

Richter's syndrome is typically abrupt in onset and characterized by rapidly progressing lymphadenopathy, splenomegaly, and systemic B symptoms [7,9–13]. The lymphomatous clone in Richter's transformation frequently arises in lymph nodes or bone marrow and disseminates to involve other organs. However, the histologic transformation may be limited to one organ, in which case the diagnosis may not be apparent. Involvement of extranodal sites such as the central nervous system, skin, or the gastrointestinal tract is not uncommon [7–13].

Histologic transformation is frequently heralded by an elevation of the serum lactate dehydrogenase (LDH), an indicator of tumor growth [7]. Other laboratory features may include the appearance of a monoclonal serum protein, lytic bone lesions, or hypercalcemia [14]. In some patients, the presence of circulating immunoblasts in the peripheral blood may be the first indication of Richter

transformation. None of these clinical or laboratory findings are specific for Richter's syndrome. However, because fever in the absence of infection and elevation of the serum LDH are infrequent in patients with CLL, their occurrence is suggestive of Richter's transformation and should prompt appropriate investigations and biopsy of suspicious lymph nodes.

Histologically, the diffuse large-cell lymphoma tends to be separate and distinct from the coexisting small lymphocytic lymphoma [8]. The involved lymph nodes show large immunoblastic cells with abundant basophilic cytoplasm, irregular nuclei, and prominent nucleoli corresponding to the Working Formulation category of large-cell immunoblastic lymphoma. Less frequently, the large-cell lymphoma cells are intimately admixed with the small lymphocytes; these cases have recently been termed the paraimmunoblastic variant of CLL/SLL [15].

Rarely, patients with CLL may develop neoplasms that morphologically and immunophenotypically resemble Hodgkin's disease (the so-called Hodgkin's variant of Richter's transformation) [16]. Although some of these cases may represent a coincidental occurrence, it has been suggested that others are examples of true transformation, mediated by the Epstein-Barr virus. In rare cases, patients with B-cell CLL have developed T-cell non-Hodgkin's lymphoma. Most likely this represents a coincidental event [17,18].

Several methods have been used to determine whether the CLL and the subsequent large-cell lymphoma are derived from the same clone. These include surface immunoglobulin typing, immunoglobulin gene rearrangement studies, and cytogenetic analysis [19–23]. Using these methods, a clonal relationship has been demonstrated in 28 of 37 well-studied cases in the literature [24]. In 9 cases, however, the CLL and the large-cell lymphoma were clonally distinct. These data suggest that about three quarters of all patients with Richter's syndrome have lymphomas that evolve from the same clone as that of the antecedent CLL, whereas the remaining patients have lymphomas that arise from a separate clone.

The genetic events involved in Richter's transformation are poorly understood. Mutations and/or allelic loss of the p53 tumor suppressor gene have been described in patients who had undergone Richter's transformation [25]. One study found that while a p53 mutation was relatively uncommon in classic B-CLL (6 of 40 cases), it was demonstrable in a significant proportion of those cases that progressed to Richter syndrome (3 of 7 cases). Another study reported that a p53 mutation was associated with progressive disease and resistance to treatment [26].

In contrast to chronic myelogenous leukemia, in which clonal cytogenetic abnormalities in addition to the Philadelphia chromosome occur almost invariably with disease progression, CLL has been considered a genetically stable disease [27,28]. Early data showed that clonal chromosomal changes were present in one half of the patients with CLL and remained stable throughout the disease course. More recently, this notion was challenged by data from prospective chromosome and gene rearrangement analyses that indicated that in 10% of the patients, leukemic B cells undergo clonal evolution over time [27]. However, no consistent chromosomal abnormalities have been reliably shown to predict or precede the development of the Richter transformation. Moreover, clonal chromosomal abnormalities frequently develop in CLL patients in the absence of any change in the clinical or laboratory parameters [28].

The occurrence of an aggressive large-cell lymphoma in CLL is similar to that in other immunodeficiency states, such as severe combined immunodeficiency, transplant patients receiving immunosuppressive drugs, and the acquired immunodeficiency syndrome [29]. The immunodeficiency state in CLL is multifactorial, involving both humoral and cell-mediated immunity. Hypogammaglobulinemia and an inversion of the physiologic ratio of CD4+ (T-helper) cells to CD8+ (T-suppressor) cells in the peripheral blood are common and both worsen in advanced stage disease. Additionally, depressed natural killer and cytotoxic T-cell activity due to a reduction in the availability of interleukin-2 has been shown to contribute to the immunologic impairment [30].

While in some patients Richter's transformation represents an independent malignancy that develops in the setting of impaired immune surveillance and is genetically unrelated to the original CLL clone, in others a common clonal origin can be demonstrated between the large-cell lymphoma and the CLL. It has been suggested that lymphomas that arise de novo have a better prognosis than those that evolve from a preexisting leukemia [31]. If this is the case, an assessment of the clonal relationship between the lymphoma and the CLL could provide prognostic information about the patient's clinical course.

The prognosis of patients with Richter's syndrome is poor, with a median survival of 5 months [7]. Patients are often treated with systemic chemotherapy and/or radiation therapy with the same regimens used to treat de novo large-cell lymphomas. A recent study found that a synchronous presentation of both malignancies was associated with a longer overall survival. This is analogous to the situation in low-grade lymphomas, in which patients with a synchronous discordant presentation of low- and high-grade histologies have a better prognosis than patients who develop histologic transformation after therapy is initiated for the low-grade lymphoma [7].

PROLYMPHOCYTIC TRANSFORMATION

Stephanie A. Gregory, MD (Director, Section of Hematology, Rush Cancer Institute)

Prolymphocytic transformation of CLL (CLL/PL) is characterized by a gradual increase in the fraction of leukemic cells resembling prolymphocytes [1]. Prolymphocytes are large cells that have abundant cytoplasm, open nuclear chromatin, and a prominent nucleolus. They express CD5 and low-intensity surface membrane immunoglobulin like the lymphocytes in CLL [1–3]. Additionally, identical surface membrane immunoglobulin isotypes and gene rearrangements have been detected in CLL cells and the prolymphocytes. These findings suggest that prolymphocytes evolve from the CLL clone. Patients with prolymphocytic transformation gradually develop anemia, thrombocytopenia, and splenomegaly in conjunction with an increase in the percentage of the prolymphocytes to 30% or more [3].

Prolymphocytic progression of CLL should be differentiated from B-cell prolymphocytic leukemia. The latter is a rare disorder associated with lymphocytosis and splenomegaly without lymphadenopathy. More than 55% of the circulating lymphocytes are prolymphocytes. Immunophenotypically, the cells express B-cell markers, CD19, CD20, and CD24. However, B-PLL cells are distinct from B-CLL in that they express bright surface immunoglobulin, infrequently express CD5, and react strongly with FMC7. In contrast to Richter's transformation, the prolymphocytic transformation of CLL has a modest effect on survival [3]. However, patients with an absolute number of prolymphocytes greater than 15×10^9/l tend to have a similar outcome as de novo B-cell prolymphocytic leukemia.

CONCLUSIONS

Indolent B-cell lymphoproliferative disorders have a propensity to ''transform'' into aggressive high-grade lymphomas. The clinical outcome of these patients with histologic transformation is poor. It is estimated that patients with CLL have a 10 times higher risk of developing another B-cell malignancy than that the normal age-adjusted population [3]. With the advent of molecular biologic techniques, it is possible to trace the origin of the large-cell lymphomas occurring in CLL. The large-cell lymphoma and the original CLL may derive from an identical clone (clonal evolution), or they may represent separate primary lymphoid neoplasms. It has been suggested that aggressive large-cell lymphomas that are clonally related to the original CLL have a worse prognosis than those lymphomas that are clonally unrelated. The latter may behave more like primary large-cell lymphomas and are associated with a better outcome. Therefore, exploring the clonal origin of aggressive lymphomas in patients with CLL may provide important prognostic information.

REFERENCES

1. Foon KA, Rai KR, Gale RP: Chronic lymphocytic leukemia: New insights into biology and therapy. Ann Intern Med 113:525–539, 1990.
2. Cheson B: Chronic lymphoid leukemias. In Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE (eds): "Clinical Oncology." Churchill Livingstone: New York, Edinburgh, London, Melbourne, Tokyo, pp. 1999–2022, 1995.
3. Foon KA, Thiruvengadam R, Saven A, et al.: Genetic relatedness of lymphoid malignancies. Transformation of chronic lymphocytic leukemia as a model. Ann Intern Med 119:63–73, 1993.
4. Minot GP, Isaacs R: Lymphatic leukemia. Age incidence, duration and benefit derived from irradiation. Boston Med Surg J 191:1–9, 1924.
5. Richter MN: Generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia. Am J Pathol 4:285–292, 1928.
6. Lortholary P, Boiron M, Ripault P, et al.: Leucemie lymphoide chronique secondairment associee a une reticulopathie maligne, syndrome de Richter. Nouv Rev Fr Hematol 4:621, 1964.
7. Robertson LE, Pugh W, O'Brien S, et al.: Richter's syndrome: A report on 39 patients. J Clin Oncol 11:1985–1989, 1993.
8. Medeiros LJ, Jaffe ES: Pathology of non-Hodgkin's lymphomas and Hodgkin's disease. In Wiernik HS, Canellos GP, Dutcher JP, Kyle RA (eds): ''Neoplastic Diseases of the Blood.'' 3rd Ed. London: Churchill Livingston, 1996, pp. 753–805.
9. Long JC, Aisenberg AC: Richter's syndrome: A terminal complication of chronic lymphocytic leukemia with distinct clinico pathologic features. Am J Clin Pathol 63:786–795, 1975.
10. Armitage JO, Dick FR, Corder MP: Diffuse histiocytic lymphoma complicating chronic lymphocytic leukemia. Cancer 41:422–427, 1978.
11. Trump DL, Mann RB, Phelps R, et al.: Richter's syndrome: Diffuse histiocytic lymphoma in patients with chronic lymphocytic leukemia. A report of five cases and report of literature. Am J Med 68:539–548, 1980.
12. Foucar K, Rydell RE: Richter's syndrome in chronic lymphocytic leukemia. Cancer 46:118–134, 1980.
13. Harrousseau JL, Flandrin G, Tricot G, et al.: Malignant lymphoma supervening in chronic lymphocytic leukemia and related disorders. Richter's syndrome: A study of 25 cases. Cancer 48:1302–1308, 1981.
14. Briones J, Cervantes F, Montserrat E, Rozman C: Hypercalcemia in a patient with chronic lymphocytic leukemia evolving into Richter's syndrome. Leuk Lymph 21:521–523, 1996.
15. Pugh WC, Manning JT, Butler JJ: Paraimmunoblastic variant of small lymphocytic lymphoma/leukemia. Am J Surg Pathol 12: 907–917, 1988.
16. Rubin D, Hudnall SD, Aisenberg A, et al.: Richter's transformation of chronic lymphocytic leukemia with Hodgkin's-like cells is associated with Epstein-Barr virus infection. Mod Pathol 7:91–98, 1994.
17. Lee A, Skelly ME, Kingma DW, Medeiros LJ: B-cell chronic lymphocytic leukemia followed by high grade T-cell lymphoma. An unusual variant of Richter's syndrome. Am J Clin Pathol 103: 348–352, 1995.
18. Brecher M, Banks PM: Hodgkin's disease variant of Richter's syndrome. Report of eight cases. Am J Clin Pathol 93:333–339, 1990.
19. Litz CE, Arthur DC, Gaje-Peczalska KJ, et al.: Transformation of

chronic lymphocytic leukemia to small non-cleaved cell lymphoma: A cytogenetic, immunological, and molecular study. Leukemia 5:972–978, 1991.
20. Van Dongen JJ, Hoojikaas H, Michiels JJ, et al.: Richter's syndrome with different immunoglobulin light chains and different heavy chain gene rearrangements. Blood 64:571–575, 1984.
21. Michiels JJ, Van Dongen JJ, Hagemeijer A, et al.: Richter's syndrome with identical immunoglobulin gene rearrangements in the chronic lymphocytic leukemia and the supervening non-Hodgkin's' lymphoma. Leukemia 3:819–824, 1989.
22. Nakamine H, Masih AS, Sanger WG, et al.: Richter's syndrome with different immunoglobulin light-chain types. Molecular and cytogenetic features indicate a common clonal origin. Am J Clin Pathol 97:656–663, 1992.
23. Cofrancesco E, Baldini L, Ciani A, et al.: Evidence of clonal progression in a case of Richter's syndrome. Cancer 71:741–744, 1993.
24. Bessudo A, Kipps TJ: Origin of high-grade lymphomas in Richter syndrome. Leuk Lymph 18:367–372, 1995.
25. Gaidano G, Ballerini P, Gong JZ, et al.: p53 mutations in human lymphoid malignancies: Association with Burkitt lymphoma and chronic lymphocytic leukemia. Proc Natl Acad Sci USA 88:5413–5417, 1991.
26. Moore JS, Friedman DF, Silberstein LE, et al.: Clinical heterogeneity reflects biologic diversity in chronic lymphocytic leukemia. Crit Rev Oncol Hematol 20:141–164, 1995.
27. Peterson L, Blackstadt M, Kay N: Clonal evolution in chronic lymphocytic leukemia. In Cheson BD (ed): ''Chronic Lymphocytic Leukemia. Scientific Advances and Clinical Developments.'' New York: Dekker, 1993, pp. 181–196.
28. Oscier DG: Cytogenetic and molecular abnormalities in chronic lymphocytic leukemia. Blood Rev 8:88–97, 1994.
29. Kay NE, Markham PD: Chronic lymphocytic leukemia: An AIDS like disease? (letter). Br J Haematol 63:389–391, 1986.
30. Foa R: Pathogenesis of the immunodeficiency in B-cell chronic lymphocytic leukemia. In Cheson BD (ed): ''Chronic Lymphocytic Leukemia. Scientific Advances and Clinical Developments.'' New York: Dekker, 1992, pp. 147–166.
31. Catovsky D: Chronic lymphoproliferative disorders. Curr Opin Oncol 7:3–11, 1995.